201-14578

COURTNEY M. PRICE
VICE PRESIDENT
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American Chemistry Council
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July 3, 2003

Via US Mail and e-mail

Linda Fisher, Acting Administrator
U.S. Environmental Protection Agency (EPA)
P.O. Box 1473
Merrifield, VA 22116

Re: Phosgene Panel,
HPV Chemical Challenge Program Submission
Phosgene (CAS Number 75-44-5)

Dear Ms. Fisher:

The Phosgene Panel ("Panel") of the American Chemistry Council is pleased to submit the attached Test Plan and supporting Robust Summary documents to EPA's HPV Chemical Challenge Program ("Program") to fill the Panel's voluntarily commitment to sponsor phosgene in the Program. Panel members are: BASF Corporation; Bayer Corporation; The Dow Chemical Company; DuPont; GE Plastics Corporation; Lyondell Chemical Company; PPG Industries, Inc.; Rubicon, Inc.; Syngenta Crop Protection (formerly Zeneca Ag Products); and VanDeMark, Inc.

This submission also is being sent electronically to the following e-mail addresses:

Oppt.ncic@epa.gov
Chem.rtk@epa.gov

If you require additional information, please contact the Phosgene Panel's technical contact, Dr. Anne P. LeHuray at (703) 741-5630 or *anne_lehuray@americanchemistry.com*.

Sincerely yours,

Attachments

Phosgene

CAS Number 75-44-5

USEPA HPV Challenge Program Test Plan Submission

July 2003

Submitted by:
Phosgene Panel
American Chemistry Council
1300 Wilson Boulevard
Arlington, VA 22009

Members:
BASF Corporation
Bayer Corporation
The Dow Chemical Company
DuPont
GE Plastics Corporation
Lyondell Chemical Company
PPG Industries, Inc.
Rubicon, Inc.
Syngenta Crop Protection
VanDeMark, Inc.

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1.0 EXECUTIVE SUMMARY

The member companies of the Phosgene Panel of the American Chemistry Council submit for review and public comment the Test Plan and Robust Summaries for phosgene (Cl_2CO (Fig. 1)) (Chemical Abstract Service (CAS) registry number 75-44-5) under the United States (U.S.) Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. The purpose of this Test Plan is to summarize available physicochemical data, environmental fate and effects, and mammalian health effects data for phosgene consistent with Screening Information Data Set (SIDS) Level 1 endpoints. Table 1 provides a summary of the adequacy of existing data for SIDS Level 1 endpoints and recommended testing for phosgene. Overall, the SIDS data set for phosgene is robust and no further toxicity testing is proposed for SIDS endpoints.

Table 1: Data Summary

Data Point	Data Available	Testing Proposed
Melting Point	Yes	No
Boiling Point	Yes	No
Vapor Pressure	Yes	No
Partition Coefficient	*	No
Water Solubility	*	No
Stability in Water	Yes	No
Transport Between Environmental Compartments	*	No
Photodegradation	Yes	No
Biodegradation	*	No
Acute Toxicity to Fish	*	No
Acute Toxicity to Invertebrates	*	No
Acute toxicity to Aquatic Plants	*	No
Acute Toxicity – Inhalation	Yes	No
Genetic Toxicity *in vivo* – Micronucleus	*	No
Genetic Toxicity *in vitro* – Ames	Yes	No
Repeat dose – inhalation	Yes	No
Reproductive Toxicity	Yes	No
Developmental Toxicity	*	No

* Not an appropriate endpoint because of lack of water stability and reactivity.

2.0 INTRODUCTION

The member companies of the Phosgene Panel of the American Chemistry Council submit for review and public comment the Test Plan and robust summaries for phosgene (CAS 75-44-5), Cl_2CO (Fig. 1), under the U.S. Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. The purpose of this Test Plan is to summarize available physicochemical data, environmental fate and effects, and mammalian health effects data for phosgene consistent with SIDS Level 1 endpoints. Based on existing data, the Test Plan contains an analysis of the need for, and appropriateness of, testing phosgene for additional SIDS endpoints.

2.1 Methods

The scientific literature and sponsor company data on the physicochemical properties, environmental fate and effects, and mammalian toxicity endpoints for phosgene was reviewed. Searches of the TOXLINE, ECOTOX, MEDLINE, and CHEMID databases were conducted using phosgene's CAS number and chemical name. Standard handbooks and databases (*e.g.,* CRC Handbook on Chemicals, IUCLID, Merck Index, *etc*.) were consulted for physicochemical properties. Robust summaries were prepared for studies to provide details of test methods and results. Several studies may have been evaluated for a particular SIDS endpoint, but robust summaries were prepared only for the critical study that represented the best available data. Selection of the critical study was based on a review of all available studies using the ranking system developed by Klimisch *et al.* (1997), as well as the criteria outlined in EPA's methods for determining the adequacy of existing data.

2.2 Production and Use

Phosgene (Figure 1) is a highly reactive gas that is classified as a Schedule 3A toxic chemical under the Chemical Weapons Convention (CWC). While produced in Europe for use as a chemical warfare agent during WWI, the Phosgene Panel is not aware that phosgene has ever been included in the U.S. chemical weapons stockpile. Phosgene is a chemical intermediate central to the production of common commercial products and deemed essential in modern day manufacturing of products used in everyday life, such as plastics, urethanes, pharmaceuticals, agricultural chemicals and specialty chemical products.

Phosgene is produced commercially from a synthesis reaction, using chlorine and carbon monoxide. Phosgene's primary use is as a raw material for production of methylene-diphenyldiisocyanate (MDI) and toluene diisocyanate (TDI). An estimated 85% of all phosgene produced is used to make MDI and TDI, which are in turn used in the production of polyurethane. About 10% of phosgene production is used to make polycarbonate plastics. The remaining 5% is used in the production of a wide variety of pharmaceuticals, agrochemicals, and specialty chemical intermediates. Polyurethane is used in the production of foam mattresses, furniture, toys, tools, coatings, rcar bumpers and fenders. Polycarbonates are used in the production of computers, telephones, optical discs, household appliances, compact discs and cassettes.

Because of its reactive and toxic properties, industrial emissions of phosgene are strictly controlled and minimized. The majority of phosgene occurring in the troposphere is produced through thermal and photochemical decomposition of various chlorinated methane, ethane, and ethylene compounds of both natural and anthropogenic origin. The magnitude of industrial phosgene emissions is considered minor compared to indirect natural sources of the chemical in the atmosphere (Helas and Wilson, 1992).

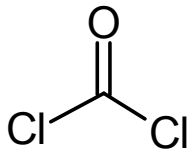

Figure 1: Phosgene

2.3 Human and Ecological Exposures

For humans, the primary route of potential exposure is by inhalation. Once inhaled, phosgene reacts with tissues of the respiratory tract to form hydrochloric acid and carbon dioxide and, therefore, only negligible amounts of inhaled phosgene are distributed in the body. Because phosgene has the potential to cause severe pulmonary irritation and, at higher doses, pulmonary edema in humans exposed by inhalation, its production is closely monitored and controlled. More than 99.9 % of phosgene produced in the U.S. is used at the facility where it is made, and is consumed in the production process. Direct industrial emissions of phosgene are minimal compared to sources from indirect photochemical reactions occurring in the troposphere (Helas and Wilson, 1992)

The boiling point of phosgene is 7.56 °C (about 40 °F). There is limited opportunity, therefore, for dermal and oral exposures to phosgene, and environmental exposures are likewise limited. Phosgene has a very short half-life (0.026 seconds) in aqueous solutions (International Programme on Chemical Safety (IPCS), 1997). Hydrolysis products of phosgene are hydrochloric acid and carbon dioxide, which are disposed of by the body through normal physiological processes. Concentrations of hydrochloric acid and carbon dioxide produced from phosgene emissions are expected to be of low ecological concern.

3.0 Test plan and Rationale

3.1 Rationale

In developing a rationale for a test plan for each SIDS Level I endpoint, data from publications and reports were evaluated for their quality using the method described by Klimisch *et al*. (1997) and professional judgment. If the reports and data were determined to be of sufficient quality, then a robust summary was prepared describing the report and data quality. In cases where data of sufficient quality to prepare a robust summary was available for a SIDS endpoint, it was concluded that no additional testing was required. For SIDS endpoints that did not have available data of sufficient quality to develop a robust summary, data from the literature were evaluated to determine if it was reasonable and technically feasible to conduct testing that would result in reproducible, defensible and meaningful data for use in hazard or risk assessments. Because of the physical and chemical properties of phosgene, it is not technically feasible to conduct certain types of tests. Attempts to conduct certain experimental studies would invariably result in inaccurate data that would not be useful in assessing the human or environmental health hazards of phosgene. The rationale for the test plan is presented in subsequent sections.

3.2 Test plan

3.2.1 Physical/Chemical Properties and Environmental Fate Studies

There are sufficient data for eight of the nine SIDS Level I physical/chemical properties and environmental fate chemistry endpoints (Table 2). Robust summaries were developed for melting point, boiling point, vapor pressure, water solubility, photodegradation, stability in water, transport between environmental compartments, and biodegradation. Secondary literature sources were used to derive values for melting point, boiling point, vapor pressure, and water solubility (IPCS, 1995). A published scientific article was used to estimate stability in water (Manogue & Pigford, 1960).

K_{ow} (partition coefficient) was the only endpoint that did not have sufficient data to support a robust summary. Although a robust summary was developed for water solubility based on an experimental study (IPCS, 1995), a water solubility value was not derived. The referenced experimental study in the robust summary demonstrated that phosgene readily reacts with water and hydrolyzes to carbon dioxide and hydrochloric acid. Phosgene was not stable in water because of its reactivity and decomposition in water. These physicochemical properties make it technically infeasible to experimentally derive a K_{ow}, therefore testing for the partition coefficient and water solubility of phosgene is not recommended. Moreover, because of rapid hydrolysis, phosgene does not persist in the environment long enough to partition into environmental compartments and, therefore, transport between environmental compartments does not apply.

Summary: Additional testing to satisfy HPV testing requirements for the physical/chemical properties and environmental fate chemistry properties of phosgene is not recommended.

Table 2: Physico-Chemical Properties/Environmental Fate Data

Data Point	Value	Reference
Melting Point	-127.8 °C	IPCS, 1995.
Boiling Point	7.56 °C	IPCS, 1995.
Vapor Pressure	1616 hPa at 20 °C	IPCS, 1995.
Water Solubility	Phosgene decomposes rapidly ($t_{1/2}$ = 0.026 sec.) in water, and therefore no accurate estimates of water solubility can be experimentally derived.	IPCS, 1995.
Photodegradation	Rates of direct and indirect photolysis of phosgene in the troposphere are negligible. The dominant process for removal of phosgene in the troposphere is hydrolytic reaction with water droplets in fog and clouds. The tropospheric hydrolysis of phosgene has been estimated over a range of latitudes, with the lifetime ranging around 10 hours, and typcially not exceeding 1 day.	Grosjean, 1991; Helas and Wilson, 1992.
Hydrolysis	Estimated half-life ($t_{1/2}$) of phosgene in water was approximately 0.026 seconds.	Manogue & Pigford, 1960
Transport Between Environmental Compartments	Fugacity modeling cannot be performed for phosgene, because of the lack of equilibrium distribution coefficients between water and other environmental media (air, soil, sediment). The transfer of phosgene vapor from air to water and soil can be derived from the aqueous- phase diffusion coefficient. This diffusion coefficient is estimated to be 1.27 x 10^{-5} cm^2/sec.	Manogue & Pigford, 1960
Biodegradation	Biodegradation is not relevant, as the material cannot co-exist with microorganisms in hydrated environmental media	Manogue & Pigford, 1960
Octanol/water partition coefficient (K_{ow})	Phosgene decomposes spontaneously in water, and therefore an equilibrium octanol/water partition coefficient cannot be derived.	IPCS, 1995.

3.2.2 Ecotoxicology

No reports or studies were found that presented data on the toxicity of phosgene to fish, aquatic invertebrates or aquatic plants. This is not surprising as phosgene is unstable and rapidly reacts with water. It is technically infeasible to conduct aquatic toxicology studies with phosgene, a

compound that hydrolyzes virtually instantaneously to form hydrochloric acid and carbon dioxide in aqueous solutions (phosgene half-life in aqueous solutions is estimated to be 0.026 seconds – Manogue & Pigford, 1960). Therefore, it is not technically feasible to conduct EPA or OECD guideline studies because of the reactive nature of phosgene in water.

For industrial use, phosgene is primarily both made and used in closed systems, and the material presents minimal probability of exposure to aquatic environments. In the unlikely event that phosgene is emitted directly to water, any associated effects on aquatic organisms will be attributed to formation of hydrochloric acid and an associated drop in pH. The acute ecological effects of hydrochloric acid have been extensively studied, and are reported in a separate IUCLID dataset. Therefore, additional studies on the ecotoxicity of phosgene are neither feasible nor proposed.

Summary: Additional testing to satisfy HPV testing requirements for ecotoxicity properties of phosgene is not recommended.

3.2.3 Mammalian Toxicology

The physical and chemical properties of phosgene, to a large measure, dictate the site and nature of health effects observed. Phosgene is expected to react rapidly with water to form carbon dioxide and hydrochloric acid. It also reacts with macromolecules containing sulfhydryl, amine and hydroxyl groups in aqueous solutions (Babad and Zeiler, 1973). Phosgene is a gas under ambient conditions, therefore the primary route of potential human exposure is inhalation. Thus, the most relevant route of exposure for toxicity testing is via inhalation. The primary toxic effects in response to both acute and repeated exposures to phosgene are focused on the portal of entry, the respiratory tract. Acute inhalation toxicity studies conclude that, at lethal concentrations, the most common findings are non-cardiogenic pulmonary edema (Frosolono and Pawlowski, 1977; Pawlowski and Frosolono, 1977; Diller *et al*., 1985) and effects on pulmonary function (Sciuto *et al*., 2002). However, the exact mechanism of phosgene toxicity is not clearly defined.

In considering whether to perform additional studies to evaluate systemic organ toxicity of phosgene, the technical feasibility of conducting studies to evaluate specific endpoints and the likelihood of acquiring useful information must be taken into account. As is characteristic of many highly reactive vapors, the portal-of-entry effects of phosgene following repeated sublethal concentrations are well documented (Kodavanti *et al*., 1997). Phosgene's physical/chemical properties mitigate against the likelihood of systemic effects. To produce adverse effects on systemic organ systems, there must be sufficient time for phosgene to traverse the aqueous surfactant layer of the lungs, the epithelial tissue, interstitium and the endothelium of pulmonary capillaries. Any unreacted phosgene entering the pulmonary capillary circulation must then be transported to the various organ systems distal to the lungs. The half-life of hydrolysis for phosgene has been experimentally determined to be 0.026 seconds and the resultant hydrolysis products are carbon dioxide and hydrochloric acid (Manogue and Pigford, 1960). Nash and Prattle (1971) have shown that the diffusion path length of phosgene in an aqueous solution is approximately 8 μm. This length is greater than the distance from the alveolar airspace to the

interior of the pulmonary capillary (about 1 μm). Thus, in a uniform aqueous medium phosgene is deemed able to diffuse across a distance sufficient to transit the gas-blood barrier.

Using a conservative assumption that the composition of surfactant and cellular constituents do not impose a greater physical impediment to diffusion of phosgene compared to a homogeneous aqueous environment, phosgene can potentially enter the blood stream following inhalation exposure. Consistent with this assumption, Sciuto *et al*. (1996) have shown that if the exposure concentration is sufficiently high, phosgene interactions with blood can be demonstrated. Any phosgene entering the systemic circulation within the lungs is still prone to rapid hydrolysis in this aqueous environment.

To examine the potential for phosgene to reach a systemic organ system unaltered, the blood circulation time in an adult rat was calculated for comparison to the half-life of phosgene. The mean measured cardiac output was 131 ml/min for a group of rats with a mean weight of 366 g (Delp *et al*., 1991). Total blood volume was estimated to be 27.08 ml for a rat with a body weight of 366 g (Brown *et al*., 1997). Using the values for total blood volume and cardiac output, circulation time in a 366 g rat is calculated to be approximately 12.4 seconds. As a first approximation, the time for phosgene to transit from the pulmonary capillaries to the heart is taken to account for 25% of the total circulation time or approximately 3.1 seconds. This time is consistent with measurements of mean transit time between the heart and the foot (approximating 25% of the complete circulation circuit) of rats with a mean weight of 340 g that was slightly greater than 3 seconds (Ishizuka, 1988). Comparing a nominal transit time from the lung capillaries to the first systemic organ (heart) of 3.1 seconds to the half-life of phosgene in an aqueous solution (0.026 sec), the transit time is equivalent to approximately 119 half-life periods of phosgene. Thus, it is not likely that phosgene absorbed by the pulmonary capillaries will reach the heart. By extension of this logic, it becomes even more remote that phosgene could reach organ systems distal to the heart such as reproductive organs (transit time is greater than 200 half-lives) and constitute a cause of concern for reproductive or developmental toxicity. The hydrolysis of phosgene is expected to lead to carbon dioxide and hydrochloric acid. The carbon dioxide will be exhaled and the buffering capacity of blood is far in excess of that required to neutralize the hydrochloric acid resulting from inhalation exposure of humans to dangerous concentrations of phosgene (Nash and Prattle, 1971).

The propensity of phosgene to induce lung damage consequently leads to secondary hypoxia, hypercapnia and acidosis following inhalation (Sciuto *et al.*, 2001). These changes in blood may influence developmental and reproductive parameters but are indirect sequelae to direct damage by phosgene of lung tissue. Thus, using animals for new studies in which exposures are at air concentrations that result in such secondary effects is not warranted in that these effects are not unique to phosgene.

In reviewing the existing database of toxicity studies for phosgene, it is concluded that there exists adequate toxicity testing of phosgene for purposes of HPV Program hazard assessment.

Three acute inhalation toxicity studies, one an OECD 403 guideline study in rats and mice, are available for the acute toxicity endpoint (Zwart *et al.*, 1990; Arts *et al.*, 1989). Thirty-minute LC_{50} values were 21 ppm in rats and 5-19 ppm in mice.

Adequate repeat dose toxicity studies, which provide sufficient data to assess repeat dose hazard from phosgene exposure, are available as well. A 12-week inhalation exposure study in rats indicates that a concentration of 0.1 ppm for 6 hrs/day, 5 days/week can be tolerated without lethality, but with some histopathologic effects in the lung (Kodavanti *et al.*, 1997). In comparison, in a 2-week repeat inhalation study in rats, there were no histopathologic effects on a wide array of systemic tissues at a phosgene exposure of 1.0 ppm for 4 hrs/day, 5 days/week (DuPont Chemical Solutions Enterprise, 1976a & b).

An OECD guideline *in vitro* genetic toxicity study of phosgene (Reichert *et al*., 1983) was considered negative, though phosgene could only be detected in the test system at cytotoxic concentrations of >10,000 ppm (*i.e.,* phosgene reacted with test system constituents at lower concentrations).

There are no reproductive, developmental, or *in vivo* genetic toxicity studies available for phosgene. However, since inhaled phosgene would react with lung tissue and macromolecules in blood, or, as discussed above, be hydrolyzed before it could even reach other relevant systemic sites or target organs ($t_{1/2}$ = 0.026 seconds, Manogue & Pigford, 1960), conducting new studies to evaluate toxicity to systemic organ systems is not expected to yield useful information and is considered both an injudicious use of experimental animals and a misallocation of other resources.

Because of the propensity for phosgene to produce portal-of-entry effects, it is likely that other systemic organ systems or tissues would be affected only at exposure concentrations that produce lung toxicity. Thus, any observed systemic effects may be secondary to direct effects on the respiratory tract.

3.2.3.1 Acute Toxicity

Acute toxicity of phosgene has been adequately evaluated in rats and mice (Zwart *et al.*, 1990; Arts *et al.*, 1989). Acute LC_{50} values for rats resulting from three different exposure durations were: 10 min = 334 mg/m^3 (83.5 ppm); 30 min = 84 mg/m^3 (21 ppm); 60 min = 49 mg/m^3 (12.25 ppm). Acute LC_{50} values for mice were generally comparable.

3.2.3.2 Genetic Toxicity

Phosgene was reported to be negative under the conditions of the Ames bacterial mutagenicity assay (liquid incubation assay with and without metabolic activation) (Reichert *et al.*, 1983). Although no specific detailed data for phosgene test results were reported, the authors concluded that the negative result was likely due to phosgene reacting rapidly in the test medium. This was verified by gas chromatographic analysis. Additional *in vitro* testing would be subject to similar technical limitations imposed by the water reactivity of phosgene, and is not proposed. As discussed above, the physical and chemical properties of phosgene precludes a valid *in vivo* test of genetic toxicity by standard procedures.

Table 3: Health Effects Data – Acute & Genotoxicity Data

Data Point	Value		Reference
Acute Oral (LD_{50}, mg/kg)	-		-
Acute Dermal (LD_{50}, mg/kg)	-		-
Acute Inhalation (LC_{50}, mg/m^3)	10 min. exp.:	334 mg/m^3 (rats) 244 mg/m^3 (fem. mice) 322 mg/m^3 (male mice)	Zwart *et al.*, 1990 Arts *et al.*, 1989
	30 min. exp.:	84 mg/m^3 (rats) 47 mg/m^3 (fem. mice) 76 mg/m^3 (male mice)	
	60 min. exp.:	49 mg/m^3 (rats) 21 mg/m^3 (fem. mice) 39 mg/m^3 (male mice)	
Genotoxicity - *In Vivo*	-		-
Genotoxicity – *In Vitro*	Phosgene is non-mutagenic under the conditions of the *S. typhimurium* test system, because it reacts rapidly in the test medium.		Reichert *et al.*, 1983

3.2.3.3 Repeat Dose Toxicity

Toxic effects of repeated exposure to phosgene have been evaluated in two complementary inhalation exposure studies. The more recent study by Kodavanti *et al*. (1997) focused on pulmonary effects. Separate groups were exposed 6 hours per day, 5 days per week as air controls or to analytically determined concentrations of 0.1 or 0.2 ppm phosgene for 4 or 12 weeks. In addition, other groups of rats were exposed for 2 days per week to 0.5 ppm or for 1 day per week to 1.0 ppm for 4 or 12 weeks. This extensive study design allowed investigation of the interaction of concentration and time of exposure. The endpoints measured were body and lung weights, lung displacement volume, histopathology of the lungs and indices of changes in lung collagen. This investigation provides a detailed description of the progression and severity of lung effects of phosgene. The focused nature of the Kodavanti *et al*. (1997) study is supplemented by an earlier study (DuPont Chemical Solutions Enterprise, 1976a & b) in which rats were exposed as air controls or to analytically determined concentrations of 0.2 or 1.0 ppm phosgene 4 hours per day, 5 days per week for two weeks. Body weights, clinical signs of toxicity, organ weights (lungs, heart, liver, kidneys, testes, spleen, thymus) and histopathology (trachea, lungs, heart, liver, kidneys, testes, epididymides, lymph nodes, spleen, thymus, sternum

(including bone marrow), thyroids, parathyroids, adrenals, pancreas, esophagus, stomach, intestine, eyes, brain and skin). No compound-related effects were observed. A direct comparison of groups exposed to, for example, the same concentration of 1.0 ppm is not reasonable because of variances in length of daily exposure, number of exposures per week and total duration of exposure. This may account for the observation of pulmonary lesions in the study by Kodavanti *et al.* (1997) and not in the earlier study (DuPont Chemical Solutions Enterprise, 1976a & b). Nevertheless, these studies confirm the findings of acute studies in that the pulmonary system is shown to be the target organ of repeated exposure phosgene toxicity and constitute a detailed investigation of the severity and progression of lesions in the target organ following repeated exposures to phosgene.

Table 4: Health Effects Data – Repeated Dose, Reproductive & Developmental Toxicity

Data Point	Value	Reference
Repeated Dose Toxicity	LOAEL = 0.1 ppm (inhalation, 12 weeks, rats)	Kodavanti *et al.*, 1997
	NOAEL > 1.0 ppm (2 weeks, inhalation, rats)	Dupont Chemical Solutions Enterprise, 1976a & b
Reproductive Toxicity	-	-
Developmental Toxicity	-	-

3.2.3.4 Reproductive and Developmental Toxicity

There are no reproductive or developmental toxicity studies of phosgene available. However, as inhaled phosgene is expected to react with lung tissues and macromolecules in blood or, alternatively, to be hydrolyzed before it could even reach relevant systemic sites or target organs, such studies would not be expected to provide a valid test for reproductive or developmental parameters. World Health Organization scientists, in the IPCS (1997) review of phosgene, concluded that "*the very short half-life (0.026 seconds) in aqueous solutions preclude a significant retention of phosgene in the body.*" In addition, since the lung appears to be the critical target organ, it is also considered likely that other systemic organ systems or tissues would be affected only at exposure concentrations that produce sufficient lung toxicity to invalidate interpretation of test results. In fact, in the 2-week repeat inhalation study cited above, male reproductive organs were not affected following phosgene inhalation. The propensity of phosgene to cause lung effects consequently led to secondary effects such as hypoxia that could influence developmental endpoints.

Summary: For purposes of satisfying HPV toxicity testing requirements for hazard assessment, it is concluded that no additional toxicity testing for the SIDS level I endpoints is necessary.

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Phosgene

Robust Summaries

CAS Number 75-44-5

Submission to the US EPA HPV Challenge Program

July 2003

Submitted by:
Phosgene Panel
American Chemistry Council
1300 Wilson Boulevard
Arlington, VA 22009

Members:
BASF Corporation
Bayer Corporation
The Dow Chemical Company
DuPont
GE Plastics Corporation
Lyondell Chemical Company
PPG Industries, Inc.
Rubicon, Inc.
Syngenta Crop Protection
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Robust Summaries

CAS Number 75-44-5

Submission to the US EPA HPV Challenge Program

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1. KLIMISCH *ET AL.* RELIABILITY CATEGORIES

The following scoring developed by Klimisch *et al.*, (1997) was used to determine the reliability of the studies referenced in this document.

Code	Category
1	Valid without restriction
2	Valid with restriction
3	Not reliable
4	Not Assignable

Subcategories

Code	Category
1	Valid without restriction
1a	GLP guideline study
1b	Comparable to Guideline study
1c	Meets National standards method (AFNOR/DIN)
1d	Meets generally accepted scientific method and is described in sufficient detail

2	Valid with restriction
2a	Guideline study without detailed description
2b	Guideline study with acceptable restrictions
2c	Comparable to Guideline study with acceptable restrictions
2d	Meets National standards method with acceptable restrictions
2e	Meets generally accepted scientific standards, well documented and acceptable for assessment
2f	Accepted calculation method
2g	Data from Handbook or collection of data

3	Invalid
3a	Documentation insufficient for assessment
3b	Significant methodological deficiencies
3c	Unsuitable test system

4	Not Assignable
4a	Abstract
4b	Secondary literature
4c	Original reference not yet available
4d	Original reference in foreign language
4e	Documentation insufficient for assessment

2. MELTING POINT

PHOSGENE (CAS# 75-44-5)

METHOD

Handbook data from International Programme on Chemical Safety (IPCS)
GLP procedures not likely followed
Reported in 1995

RESULTS
Melting Point = – 127.8°C

Data from selected secondary literature state melting point to be – 118°C (The Merck Index, 1987; Dupont Chemical Solutions Enterprise, 1984); –127.8°C (Schneider & Diller, 1991; Hardy, 1982); - 180°C (EPA, 1985); and –104°C (Perry & Green, 1997). The secondary sources range from –104°C to –180°C, and they do not describe methodology or experimental procedures.

CONCLUSION
The melting point value reported by the IPCS (1995) is within the range of other values reported in the secondary literature.

DATA QUALITY
Reliability code = 2 (2G). The melting point value is derived from a well-documented, reliable publication.

REFERENCE
IPCS, 1995

3. BOILING POINT

PHOSGENE (CAS# 75-44-5)

METHOD

Handbook data from International Programme on Chemical Safety (IPCS)
GLP procedures not likely followed
Reported in 1995

RESULTS
Boiling Point = 7.56°C

Data from selected secondary literature state boiling point to be 7 °C (Daubert & Danner, 1985, 1989); and 8.2°C (EPA, 1985; Perry & Green, 1985). The secondary sources do not describe methodology or experimental procedures.

CONCLUSIONS
The boiling point value is similar to other values reported in the secondary literature.

DATA QUALITY
Reliability code 2 (2G). The boiling point value is derived from a well-documented, reliable publication.

REFERENCE
IPCS, 1995.

4. VAPOR PRESSURE

PHOSGENE (CAS# 75-44-5)

METHOD

Handbook data from International Programme on Chemical Safety (IPCS)
GLP procedures not likely followed
Reported in 1995

RESULTS
Vapor Pressure value is 1616 hPa (161.6 kPa) at 20°C.

Additional data from secondary literature state vapor pressure is 1215 mm Hg at 20°C (The Merck Index, 1987), and 157.3 kPa at 20°C (Phosgene Summary Document # 15091). Other secondary sources are in the same range.

CONCLUSIONS
The vapor pressure value is similar to ranges found in other secondary literature references.

DATA QUALITY
Reliability code = 2 (2G). The vapor pressure value is derived from a reliable, well-documented publication.

REFERENCE
IPCS, 1995.

5. WATER SOLUBILITY

PHOSGENE (CAS# 75-44-5)

METHOD

Handbook data from International Programme on Chemical Safety (IPCS)
GLP procedures not likely followed
Reported in 1995

RESULTS

Phosgene decomposes rapidly in water, and therefore no accurate estimates of water solubility can be experimentally derived.

CONCLUSION

Phosgene readily reacts with water and hydrolyzes very rapidly. Data from numerous handbooks report that phosgene hydrolyzes rapidly in aqueous solutions to carbon dioxide and hydrochloric acid. The half-life in water has been estimated at 0.026 seconds (Manogue and Pigford, 1960), which precludes accurate estimates of water solubility.

DATA QUALITY

Reliability code = 2 (2G).

REFERENCE

IPCS, 1995.

6. PHOTODEGRADATION

PHOSGENE (CAS# 75-44-5)

METHOD
Direct Photolyis:
- Accepted estimation procedures
- Study on phosgene sources and sinks in the atmosphere
- GLP procedures not used
- Study reported in 1992

Indirect Photolysis:
- Laboratory experimental procedures
- Study on phosgene gas reaction with hydroxyl radicals
- GLP procedures not used
- Study reported in 1988

RESULTS
Direct Photolysis:

Helas and Wilson (1992) estimate a half-life for direct photolyis of phosgene ranging from 13 to 36 years, based on an assumed quantum yield of 1 and noon actinic fluxes at equinox for 45° N latitude.

Indirect Photolysis
The rate constant for reaction of phosgene with photochemically generated hyrdoxyl radical was determined by Witte and Zetsch (1988) to be 3.8×10^{-16} cm^3-$molecule^{-1}$-sec^{-1}. Using the EPA-accepted average hydroxyl radical concentration of 1.5×10^6 molecule-cm^{-3} (EPIWIN, 2000), the half-life for indirect pholoysis is estimated to be in excess of 77 years.

CONCLUSION
Phosgene does not react appreciably with photochemically produced hydroxyl radicals (IPCS, 1995). Direct and indirect photolysis in air is negligible under irradiation conditions approximating those of sunlight (Grosjean, 1991). The dominant process for removal of phosgene in the troposphere is hydrolytic reaction with water droplets in fog and clouds. The tropospheric hydrolysis of phosgene has been estimated over a range of latitudes (Helas and Wilson, 1992). The estimated troposhperic lifetime ranges around 10 hours, and is not believed to exceed 1 day. Dry deposition of phosgene vapor to surface water, soil, and vegetation also contributes to shortened lifetimes of the chemical in the troposphere. Lifetimes of approximately 7 days are attributed to this deposition process (Helas and Wilson, 1992).

DATA QUALITY
Reliability code = 2 (2E, 4D)

REFERENCES

Helas, G. and S. R. Wilson. 1992. On sources and sinks of phosgene in the troposphere. *Atmospheric Environment* 26A(16):2975-2982.
Witte, F. and C. Zetsch. 1988. Messung der Reaktion von asugewahlten umweltrelevanten Altstoffen. *Schlubber.* UBA, November 1988.

7. STABILITY IN WATER

PHOSGENE (CAS# 75-44-5)

METHOD

Laboratory experimental procedures
Study on phosgene gas dissolved in aqueous solutions
GLP procedures not used
Study reported in 1960

RESULTS

Phosgene dissolved in shore laminar jets of aqueous solutions decomposed rapidly. Rate constants for hydrolysis to were estimated in a series of experiments in water and in sodium nitrate and sodium hydroxide solutions at 25°C.

Estimated half-life of phosgene in water was approximately 0.026 seconds.

Phosgene hydrolyzed to carbon dioxide and hydrochloric acid in aqueous solutions.
The lack of stability of phosgene in water due to rapid hydrolysis is substantiated by other laboratory studies on the gas phase hydrolysis of phosgene (Butler and Snelson, 1979).

CONCLUSIONS

Phosgene undergoes rapid hydrolysis in aqueous solutions. It is sparingly soluble in water and reacts with water very rapidly. These characteristics make it difficult to accurately define water solubility estimates and octanol-water partition coefficients. Modeled data (EPIWIN) for water solubility and partition coefficients provide inaccurate estimates for these parameters because the models do not take into account the rapid hydrolysis of phosgene in aqueous solutions.

REFERENCE

Manogue and Pigford, 1960.

8. TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS (FUGACITY)

PHOSGENE (CAS# 75-44-5)

METHOD

Laboratory experimental procedures
Study on phosgene gas dissolved in aqueous solutions
GLP procedures not used
Study reported in 1960

RESULTS

Aqueous-phase diffusion coefficient estimated as 1.27×10^{-5} cm^2-sec^{-1}

CONCLUSION

Equilibrium distribution coefficients, such as the octanol-water partition coefficient (K_{ow}), air-water partition coefficient (K_{aw}), and octanol-air partition coefficient (K_{oa}) are commonly used to predict the distribution and transport of a chemical among air, water, soil, and sediment compartments of the environment. The Level I and Level III fugacity models, developed by Mackay, provide a convenient means of applying these equilibrium distribution coefficients in determining the environmental distribution and transport of a chemical under equilibrium (level I) and non-equilibrium steady-state (level III) conditions. However, due to the virtually instantaneous reaction of phosgene in water, the transport of the material between environmental compartments cannot be predicted using equilibrium distribution coefficients involving the water phase. Environmental media such as clouds, surface water, surface soils, and vegetation will act as sinks for removal of atmospheric phosgene emissions. The rates of these reactions are governed by the kinetics of diffusion from the gas phase into these media, rather than by chemical equilibrium between the gas and condensed water phases. Therefore, the liquid-phase diffusion coefficient, as reported by Manogue and Pigford (1960) is a key parameter for determining transport of phogene from the atmosphere to condensed aqueous phases.

DATA QUALITY
Reliability code = 2 (2e)

REFERENCE
Manogue and Pigford, 1960.

SUPPLEMENTAL REFERENCES

64-Helas, G. & S.R. Wilson.-On sources and sinks of phosgene in the troposphere.-1992-Atmos Environ 26A: 2975-82.

135-WHO-Environmental Health Criteria 193. Phosgene-1997-WHO. Environmental Health Criteria; 193; Phosgene. XVII+70. WHO: Geneva, Switzerland. ISBN 92-4-157193-4.; 193 (0). 1997.XVII+ 70p.

145--Environmental Health Criteria for Phosgene. Second Draft.-1995-International Programme on Chemical Safety PCS/EHC.94.47, Oct. 1995.

80-Kindler, T.P. et al.-The fate of atmospheric phosgene and the stratospheric chlorine loadings of its parent compounds: CCL4, C2CL4, C2HCL3, CH3CCL3, and CHCL3.-1995-J Geophys Res 100: 1235-51.

9. BIODEGRADATION

PHOSGENE (CAS# 75-44-5)

METHOD

Laboratory experimental procedures
Study on phosgene gas dissolved in aqueous solutions
GLP procedures not used
Study reported in 1960

RESULTS

CONCLUSIONS

Biodegradation occurs only in environmental compartments that contain liquid water (e.g. surface waters, sediments, wet soils). Hydrolysis of phosgene occurs instantaneously in these media, with a measured half-life on the order of 0.026 seconds (Manogue and Pigford, 1960). Biodegradation is therefore not a relevant fate process for phosgene.

DATA QUALITY

Reliability code = 2 (2e)

REFERENCE

Manogue and Pigford, 1960

10. ACUTE TOXICITY

PHOSGENE (CAS# 75-44-5)

Source and chemical characterization of phosgene not reported.

METHODS

Method/guideline:	OECD guideline #403
Type:	Acute lethality
GLP (Y/N):	Yes
Year study performed:	1989/90
Species/strain:	SPF-bred Wistar rats; Swiss mice
Sex:	Males and females for both rats and mice
Number of animals: concentration	5 males and 5 females for each species at each exposure time and
Route of administration:	Inhalation
Age:	Rats – 5-6 weeks (150-170 grams/males, 130-140 grams/females)
	Mice – 7-8 weeks (28-34 grams/males, 23-27 grams/females)
Doses per time period:	8 doses/5 min, 7 doses/10 min, 5 doses/30 min, 4 doses/60 min
Concentrations:	Ranged from 26 to 856 mg/m^3 (6.5 to 214 ppm)
Exposure durations:	5, 10, 30 or 60 minutes

Post dose observation period: 1,2,4,7 and 14 days

Study design: All rats were autopsied for gross pathological lesions

RESULTS

Mortality rates for rats and mice are reported for each sex at each time and concentration

Calculated LC_{50} values (95% confidence intervals) are given for 10, 30, and 60 minute exposures as follows:

10 min exposures		
Rat (male/female combined)	334	(306-363) mg/m^3
Mouse (male)	322	(269-394) mg/m^3
Mouse (female)	244	(201-304) mg/m^3
30 min exposures		
Rat (male/female combined)	84	(77-92) mg/m^3
Mouse (male)	76	(61-93) mg/m^3
Mouse (female)	47	(30-61) mg/m^3
60 min exposures		
Rat (male/female combined)	49	(45-54) mg/m^3
Mouse (male)	39	(29-51) mg/m^3
Mouse (female)	21	(12-30) mg/m^3

Description, severity, time of onset and
duration of clinical signs at each dose level: Not described

Necropsy findings: Not described

CONCLUSIONS
The LC_{50} values for rats (males/females combined) and male mice are comparable at each exposure time, but the values for male mice appear greater than those for female mice at each exposure time. The acute toxicity of phosgene has been studied extensively, as is apparent from the lengthy list of referenced studies, and the LC_{50} values are generally consistent.

DATA QUALITY
Reliability code = 1 (1a) – (Guideline study without restrictions)

REFERENCES
Zwart *et al.*, 1990. [mice and rat data]

Arts *et al.*, 1989. [rat data only]

Note: Same rat data and conclusions are reported in both referenced studies.

11. GENETIC TOXICITY IN VITRO (GENE MUTATIONS)

TEST SUBSTANCE
Phosgene (CAS# 75-44-5)
Source of phosgene and other test materials are provided, but no analysis of purity is given

METHODS
Method/guideline followed: OECD guideline for Ames assay bacterial mutagenicity study, using the liquid incubation procedure.

Type:	Reverse mutation assay
System of testing:	Bacterial
GLP:	GLP claims not specified, but documentation and test conditions appear to meet at least the spirit of GLP.
Year study performed:	1983
Species/Strain:	*Salmonella typhimurium* strains TA 98 and TA 100
Metabolic activation:	Liver S9 was prepared from Aroclor 1254 (500 mg/kg)-treated rats as described by Ames *et al.* (1975). Mutagenicity was assessed with and without the S9 rat liver activation system.
Concentration tested:	Not specified, but unchanged phosgene was detected in the incubation medium by GC analysis only above a gaseous concentration of 10,000 ppm.
Statistical methods:	Not specified, although data points in graphs have brackets to indicate variability
Specific test conditions:	Phosgene vapors were prepared at various concentrations in nitrogen and bubbled through the liquid suspension medium. However, the report is predominantly a presentation of methods and results for dichloroacetylene, which rapidly decomposes to several products including phosgene.

RESULTS
No specific mutagenicity results are reported for phosgene. However, the authors state: "Phosgene is non-mutagenic under the conditions of the *S. typhimurium* test system, because it reacts rapidly in the test medium. We detected unchanged phosgene in the solution only above a gaseous concentration of 10,000 ppm."

CONCLUSIONS

Phosgene would not be mutagenic under the conditions of liquid suspension in the Ames assay, because this volatile gas reacts rapidly and completely with the components of the incubation system. This does not allow measurable exposure concentrations of phosgene to be attained in the test system. Thus, the extreme reactivity and toxicity of phosgene obviates the feasibility of further genetic toxicity testing.

DATA QUALITY
Reliability code = 2 (2C) – (Comparable to guideline study with acceptable restrictions). Report appears adequate for hazard assessment, based on the above conclusions. The quality of the report for methods and results of dichloroacetylene and the other materials tested strongly supports the credibility of the authors' conclusion.

REFERENCE
Reichert *et al.,* 1983.

12. REPEATED DOSE TOXICITY

TEST SUBSTANCE
Phosgene (CAS# 75-44-5)

Source and chemical characterization of phosgene not reported.

METHOD
Method/guideline followed: Experimental study to investigate lung effects, not an OECDguideline study

Test type:	12-week inhalation toxicity study.
GLP:	Study appears to be in compliance with GLP, since conducted by USEPA laboratory
Year study performed:	1997
Species:	Rat
Strain:	Fischer 344
Route of administration:	Inhalation
Duration of test:	4 or 12 weeks for all dose levels
Doses/concentration level:	0.1, 0.2, 0.5, 1.0 ppm
Exposure period:	6 hrs/day
Frequency of treatment:	0.1 ppm for 5 days/week; 0.2 ppm for 5 days/week; 0.5 ppm for 2 days/week; 1.0 ppm for 1 day/week
Sex:	males only
Control group and treatment:	clean air only 5 days/week for 4 or 12 weeks
Post-exposure observation period:	One group of rats exposed for 12 weeks were allowed to recover for 4 weeks. Other two groups exposed for 4 or 12 weeks were evaluated after the last exposure to phosgene
Statistical methods:	multivariate analysis of variance [MANOVA]
Study design:	Only effects on the lung were investigated. These included lung weight and displacement volume, lung

histopathology, and biochemical assays (hydroxyproline and desmosine analysis).

RESULTS

NOAEL: None

LOAEL: 0.1 ppm (based on lung weight and displacement volume)

Toxic response/effects by dose level: No lethality was reported in any of the exposed groups Lung weight and displacement volume were significantly changed at 4 weeks, even at the 0.1 ppm exposure concentration. There was no further change at 12 weeks.

Pulmonary histological changes [thickening and inflammation] were associated with phosgene exposure, at the terminal bronchiolar regions at 0.1 and 0.2 ppm concentrations, and in the more peripheral areas at 1.0 ppm [the 0.5 ppm samples were inadvertently lost]. The severity of changes seemed to depend on phosgene concentrations, and not concentration X time of exposure.

Histopathology following 4 weeks of clean air recovery after 12 weeks of phosgene exposure indicated almost complete recovery at 0.1 ppm; the 0.2 ppm group appeared to have resolved considerably; collagen staining remained at the same level of intensity in the 12 weeks group at 0.2 and 1.0 ppm.

CONCLUSIONS
The authors conclude that daily exposure to 0.1 ppm phosgene for 6 hrs/day, 5 days/week, for 4 and 12 weeks can cause subtle histological changes in the lungs of rats. Higher concentrations cause more pronounced effects, which appear to depend more on phosgene concentration than time of exposure. No lethality was reported.

DATA QUALITY
Reliability = 2 (2C) – (Comparable to guideline study with acceptable restrictions). EPA study was well conducted and reported, but restrictions are that only male rats were used.

REFERENCE
Kodavanti *et al.*, 1997.

13. REFERENCES

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